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(21) International Application Number: PCT/US96/08492 (22) International Filing Date: 3 June 1996 (03.06.96) (30) Priority Data: 08/484,294 7 June 1995 (07.06.95) US (71) Applicant: CYGNUS, INC. [US/US]; 400 Penobscot Drive, Redwood City, CA 94063 (US). (72) Inventors: LI, Chunhua; 19688 Vicksburg Drive, Cupertino, CA 95014 (US). SCHONFELD, Edward; 85 Dodds Lane, Princeton, NJ 08540 (US). CHU, Tara; 1714 Banff Drive, Sunnyvale, CA 94087 (US). CHIANG, Chia-Ming; 380 Shad Court, Foster City, CA 94404 (US). (74) Agents: KONSKI, Antoinette, F. et al.; Morrison & Foerster L.L.P., 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: PRESSURE SENSITIVE ACRYLATE ADHESIVE COMPOSITION CROSS-LINKED WITH ALUMINUM ACETYLACETONATE AND CONTAINING A DRUG HAVING A REACTIVE AROMATIC HYDROXYL GROUP (57) Abstract Non-yellowing organic solvent based pressure sensitive acrylate adhesives that have good cohesive strength and cold flow properties and are useful in fabricating transdermal drug delivery patches are made from an organic solvent based pressure sensitive acrylate adhesive cross-linked with aluminum acetylacetonate and combined with a drug, such as estradiol, that has a reactive aromatic hydroxyl group.		

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PRESSURE SENSITIVE ACRYLATE ADHESIVE COMPOSITION
CROSSLINKED WITH ALUMINUM ACETYLACETONATE AND CONTAINING
A DRUG HAVING A REACTIVE AROMATIC HYDROXYL GROUP

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Description

Technical Field

The present invention relates to transdermal drug delivery patches.

10 More particularly it concerns a matrix type transdermal drug delivery patch whose matrix comprises a mixture of a pressure sensitive acrylate adhesive crosslinked with aluminum acetylacetonate and a drug, such as estradiol, which has a reactive aromatic hydroxyl group.

15 Background

Transdermal drug delivery patches normally include a backing layer that forms the outer face of the patch, a drug reservoir underlying the backing layer, and means to affix the patch to the skin. The drug reservoir may be a liquid solution or suspension of the drug or a solid matrix of a drug-carrier mixture. The carrier of the
20 solid matrix may be an adhesive or have nonadhesive properties. If it is adhesive, the matrix may serve as the means for affixing the patch to the skin. If it is not adhesive, an in-line adhesive layer may underlie the matrix for affixing the patch to the skin. If the reservoir is a liquid, the patch will often include a drug-permeable membrane that underlies the reservoir and an in-line adhesive layer that underlies the membrane.

25 Pressure sensitive adhesives are often used as the adhesive in the above-described patches. Pressure sensitive adhesives are used either as the carrier of the drug-containing matrix or as a separate in-line adhesive layer. In either instance the pressure sensitive adhesive will be admixed with drug.

Solution polyacrylate adhesives are one type of pressure sensitive adhesive that are used in transdermal drug delivery patches. Solution polyacrylates are made by copolymerizing one or more acrylate monomers, a modifying monomer and a monomer containing functional groups in a solution of an organic solvent.

5 2-Ethylhexylacrylate, butylacrylate and isooctylacrylate are commonly used as the acrylate monomer. The polyacrylate may be crosslinked or uncrosslinked.

Crosslinked acrylate adhesives generally have better cohesive strength and resistance to cold flow than uncrosslinked acrylate adhesives. Increased cohesive strength is desirable in transdermal uses of acrylates to reduce the mass transfer of adhesive to the skin when the patch is removed. Resistance to cold flow is desirable to prevent the adhesive from oozing from the patch during storage or wear. Accordingly, crosslinked solution polyacrylates are preferred.

U.S. 5,393,529 describes an adhesive matrix type transdermal patch for delivering estradiol or estradiol esters. The adhesive of the matrix may be a crosslinked or uncrosslinked solution polyacrylate containing a water-swellaable polymer. Aluminum acetylacetonate is included in a list of possible agents for crosslinking the polyacrylate.

U.S. 5,292,951 describes estrogen-containing gels for topical application. The gels are comprised of estrogen, crosslinked acrylate polymers and relatively large amounts of a fat or oil that serves as an estrogen solubilizer.

Applicants have found that the selection of crosslinking agent is critical to preparing adhesive compositions of estradiol or other drugs that have a reactive aromatic hydroxyl group that will not develop an objectionable color and have the desired cohesive strength and cold flow properties discussed above.

25 Accordingly, the present invention provides an adhesive composition comprising a crosslinked pressure sensitive acrylate adhesive mixed with an aromatic hydroxy-containing drug that does not develop objectionable color and has good cohesive strength and cold flow properties.

Disclosure of the Invention

One aspect of the invention is a pressure sensitive adhesive composition useful in a transdermal drug delivery patch comprising a mixture of:

- a) a drug having a reactive aromatic hydroxyl group; and
- 5 b) an aluminum acetylacetonate crosslinked solution polyacrylate pressure sensitive adhesive.

Another aspect of this invention is a transdermal drug delivery patch in the form of a laminated composite comprising:

- (a) a backing layer that forms the top surface of the patch; and
- 10 (b) a matrix layer underlying the backing layer that comprises:
 - (i) a drug having a reactive aromatic hydroxyl group; and
 - (ii) an aluminum acetylacetonate crosslinked acrylate pressure sensitive adhesive.

15 Modes for Carrying Out the Invention

The pressure sensitive adhesive component of the invention compositions and patches is a solution polyacrylate. Such polyacrylates are made by copolymerizing one or more main acrylate monomers ("acrylate" is intended to include both acrylates and methacrylates), one or more modifying monomers, and one or more
20 functional group-containing monomers in an organic solvent solution. The acrylate monomers used to make these polymers are normally alkyl acrylates of 4-17 carbon atoms, with 2-ethylhexylacrylate, butylacrylate and isooctylacrylate being preferred. Modifying monomers are typically included to alter the Tg of the polymer. Examples of modifying monomers are acrylates such as ethyl acrylate, vinyl acetate, and methyl
25 methacrylate. The functional group-containing monomer provides sites for crosslinking. In the polyacrylate of the present invention, the functional group(s) will normally be carboxyl, hydroxyl, or combinations thereof. Monomers that provide such groups are acids, e.g. acrylic acid, and hydroxy-containing monomers such as hydroxyethyl acrylate. Examples of such solution polyacrylates are disclosed in the art.
30 See, for instance, U.S. 5,393,529, the disclosure of which with respect to such

copolymers is incorporated herein. Preferred copolymers are those of 2-ethylhexylacrylate, vinyl acetate, hydroxyethylacrylate, and glycidyl methacrylate.

The drug component of the invention composition is a drug that has a reactive aromatic hydroxyl group. The term "aromatic hydroxyl group" intends a hydroxyl or hydroxyimino group that is attached directly to an annular carbon atom of a mono- or polycyclic aromatic moiety. Examples of such drugs are 17 β -estradiol, 17 α -estradiol, 17 β -estradiol cypionate, ethinyl estradiol, 3,17 β -estradiol dienanthate, 17 β -estradiolvalerate, 17-deacetyl norgestimate, and norgestimate. Other drugs may be included in the composition. For instance when the aromatic hydroxy-containing drug is estradiol, progestogens and/or androgens may be included. The aromatic hydroxy-containing drug will usually constitute between about 0.5% and 10% by weight of the adhesive composition.

According to the present invention the acrylate adhesive is crosslinked with sufficient aluminum acetylacetonate to significantly improve the cohesive strength and cold flow properties of the adhesive relative to those of the uncrosslinked adhesive. The crosslinking density should be low since high degrees of crosslinking may adversely affect the tack and pull adhesion or yield a nontacky product. Normally the amount of aluminum acetylacetonate used is in the range of 0.1 to 1% by weight.

The adhesive composition is crosslinked by mixing a solution of the polyacrylate, aluminum acetylacetonate, and drug in the desired proportions, causing the mixture to effect crosslinking, and then removing the solvent. Examples of solvents that may be used are ethylacetate, ethanol, methanol, toluene, isopropyl alcohol and heptane. The curing will normally be carried out at 50 to 150°C for 1 to 20 minutes.

As indicated above, the adhesive compositions of the invention may be used to form the matrix (drug reservoir) component of a transdermal patch or be used as a separate in-line adhesive layer. In either application, the composition defines the basal surface (i.e. the surface that contacts the skin) of the patch when the patch is in use. As indicated, when the composition is used to form the matrix, the drug is incorporated into the adhesive before crosslinking. When the composition forms an in-line basal adhesive layer, the drug may be incorporated into the layer either before crosslinking or by equilibration after the patch has been assembled.

The compositions of this invention are unexpectedly substantially free of objectionable yellowing or other coloring. In this regard the use of other metallic acetylacetonates as crosslinking agents were found to produce colored compositions, or unacceptably high or low levels of crosslinking. In addition the composition possesses acceptable cohesive strength and cold flow properties. Cohesive strength may be determined by a dynamic viscosity test. Cold flow may be observed visually. Normally the cold flow is observed after storage of the patch at elevated temperatures (e.g. 450C) for several months.

The following examples further illustrate the invention. These examples are not intended to limit the invention in any manner. Unless indicated otherwise, stated percentages in the examples are by weight.

Example 1. Preparation of Adhesive of Duro-Tak 2287, Aluminum Acetylacetonate and 17 J-estradiol.

Duro-Tak 87-2287 is a solution polyacrylate available from National Starch and Chemical Company. It contains no crosslinking agent. (Its monomer composition is vinyl acetate; 2-ethylhexylacrylate; hydroxyethylacrylate; and glycidyl methacrylate.) It is available as a 50% by weight solids solution in ethyl acetate.

A solution of Duro-Tak 87-2287 was mixed with 0.5% aluminum acetylacetonate, and 3% 17 β -estradiol. The mixture was cured at 900C for 2 min. and cast onto a release liner and the solvent was dried off. Cohesive strength tests were carried out on a sample of the mixture using a dynamic viscosity test. Its dynamic viscosity was $5.00E + 07$. The dynamic viscosity is measured using Refleometrics Dynamic Spectrometer (RDS). The cured sample is placed between parallel plates in the RDS, and their dynamic viscosity measured at a frequency of 0.001 rad/sec.

Skin flux tests were carried out on the above-described Duro-Tak 87-2287/estradiol and backing assembly according to the procedure described in Col. 7 of U.S. 5,252,334. The flux of drug from the assembly was $0.6 \pm 0.1 \mu\text{g}/\text{cm}^2/\text{hr}$.

The cold flow properties of the assembly were tested by storing the assembly at 450C for 3 mos. No cold flow of the adhesive layer was observed.

The adhesive layer of the patch remains uncolored after storage at 450C for 3 mos.

For comparison purposes, patch assemblies were made from Duro-Tak 87-2287 and 3% estradiol without crosslinking agent. These assemblies exhibited poor dynamic viscosity ($1.79E + 07$). The adhesive remains clear after storage but cold flow was observed.

Example 2. Comparison Preparations of Polyacrylate Crosslinked With Other Metallic Acetylacetonates and 17 β -estradiol.

10 Duro-Tak 87-2516 is a solution polyacrylate available from National Starch and Chemical Company. Its monomer composition is the same as Duro-Tak 87-2287 but it contains polybutyl titanate crosslinker. It is available as a solution in a solvent system of ethylacetate/ethanol/heptane/methanol.

15 Mixtures of Duro-Tak 87-2516 and 3% estradiol were prepared and cured as in Example 1. The mixture was cast into a release liner as in Example 1 and dried. The cured mixture and assembly were tested as in Example 1. The results were: dynamic viscosity, $5.00E + 07$; E2 flux, $0.5 \pm 0.04 \mu\text{g}/\text{cm}^2/\text{hr}$; no cold flow; distinct yellow color.

20 Modification of the above-described modes for carrying out the invention that are obvious to those of skill in the fields of transdermal patch and/or pressure sensitive adhesives are intended to be within the scope of the following claims.

Claims

1. A pressure sensitive adhesive composition useful in a transdermal drug delivery patch comprising a mixture of:
 - a) a drug having a reactive aromatic hydroxyl group; and
 - b) an aluminum acetylacetonate crosslinked solution polyacrylate pressure sensitive adhesive.
2. The composition of claim 1 wherein the drug is 17 β -estradiol, an ester of 17 β -estradiol, α -estradiol, norgestimate, or 17-deacetyl norgestimate.
3. The composition of claim 2 wherein the acrylate adhesive is a copolymer of 2-ethylhexyl acrylate, vinyl acetate, hydroxyethyl acrylate and glycidyl methacrylate.
4. The composition of claim 1 wherein the drug constitutes 0.5% to 10% by weight of the composition, and the aluminum acetylacetonate constitutes 0.1% to 1% by weight of the composition.
5. The composition of claim 3 wherein the drug constitute 0.5% to 10% by weight of the composition, and the aluminum acetylacetonate constitutes 0.1% to 1% by weight of the composition.
6. A transdermal drug delivery patch in the form of a laminated composite comprising:
 - (a) a backing layer that forms the top surface of the patch; and
 - (b) a matrix layer underlying the backing layer that comprises:
 - (i) a drug having a reactive aromatic hydroxyl group; and
 - (ii) an aluminum acetylacetonate crosslinked acrylate pressure sensitive adhesive.

7. The patch of claim 6 wherein the drug is 17 β -estradiol, an ester of 17 β -estradiol, α -estradiol, norgestimate, or 17-deacetyl norgestimate.

5 8. The patch of claim 7 wherein the acrylate adhesive is a copolymer of 2-ethylhexyl acrylate, vinyl acetate, hydroxyethyl acrylate and glycidyl methacrylate.

9. The patch of claim 6 wherein the drug constitutes 0.5% to 10%
10 by weight of the composition, and the aluminum acetylacetonate constitutes 0.1% to 1% by weight of the composition.

10. The patch of claim 8 wherein the drug constitute 0.5% to 10% by
weight of the composition, and the aluminum acetylacetonate constitutes 0.1% to 1%
15 by weight of the composition.